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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/659,178	09/09/2003	David Jonathan Madge	2451.0090006	7469

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WASHINGTON, DC 20005

EXAMINER

VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
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1621

MAIL DATE	DELIVERY MODE
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05/23/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/659,178

Applicant(s)

MADGE ET AL.

Examiner

Yevgeny Valenrod

Art Unit

1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-64 is/are pending in the application.
- 4a) Of the above claim(s) 24,25 and 29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-23,26-28 and 30-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

Rejection of claim 11 under 35 USC 112 2nd paragraph is withdrawn in view of applicants' amendment.

Rejection of claims 1-18, 21, 22, 23, 26-28 and 30-36 under 35 USC 103(a) is maintained. The text of the rejection has been amended to include the newly added claims 39, 43 and 44.

Nonstatutory obviousness-type double patenting rejection of claim 1-23, 26-28 and 30-38 is maintained.

Newly added claims 39-64 are rejected on the ground of nonstatutory obviousness-type double patenting over US 7,112,572 ('572). Text of the double patenting rejection is repeated below. The text has been amended to include the newly added claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-18, 21, 22, 23, 26-28 and 30-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rewinkel et al. (Current Pharmaceutical Design, 1999, 5, 1043-1075) in view of de Nanteuil et al. (US 5,814,622) and in further view of Adams et al. US 5,780,454).

Instant claims 1-18, 21, 22, 23, 26-28 and 30-36 are directed to a pharmaceutically acceptable base addition salt of a boronic acid of formula (I) in claim 1, or formula (II) in claim 14 and to formulation of the said salt in claims 26-28.

Scope of prior art

Rewinkel et al. teach a compound of formula 21 (page 1052, bottom left of Table 3). The said compound is a boronic acid that has the methoxyalkyl substituent for R⁹ in the instant claim 1, a Pro amino acid residue, which satisfies the structural limitation of claim 17, a hydrophobic moiety presented by the diphenylalanine residue, and a protected N-terminal amine group. Renkwel et al. Provide K_i for thrombin inhibition in the table on the bottom of page 1052. Compound 21, has K_i of 14 nM, which is below 100nM as claimed in claims 7 and 28.

Ascertaining the difference between prior art and the instant claims

Rewinkel et al. teach the organic component of the instantly claimed organoboronic acid salt. They also teach the boronic acid attached to the organic component in a position consistent with the structural limitations of the instant claims. However, they fail to teach the pharmaceutically acceptable salt of the boronic acid.

Secondary reference

Nanteuil et al. Describe compound of formula (I/g) (organoboronic acid) and pharmaceutically acceptable salts thereof (column 6, lines 20-36). The pharmaceutically acceptable salts include both base and acid addition salts. In Column 3, lines 32-34 Nanteuil et al. describe examples of counterions for base addition salts. Said examples include Sodium, Potassium and amines.

Motivation and obviousness

It is obvious to form salts from known acids. In re Williams, 89 USPQ 396 (CCPA 1951). Rewinkel et al. teach compound 21, which is the acid of the instantly claimed pharmaceutically acceptable salt. At the time the instant invention was made, one of ordinary skill in the art looking to alter the permeability, solubility, or other physiological properties commonly associated with producing pharmaceutically acceptable salts of known acid (see Davies et al, The pharmaceutical journal, 2001, Vol 266, p 322-323; particularly page 322, column 1, first paragraph) would have been motivated to prepare a salt of the organoboronic acid 21 described by Rewinkel et al. Such a modification would not be new to the art. Nanteuil et al describe pharmaceutically acceptable salts of organoboronic acids and thus provide an expectation of success for performing the said modification. Nanteuil et al. do not limit themselves to the counterion examples that are listed in column 3 lines 32-34. They specifically mention that these examples are provided without any limitation. One of ordinary skill in the art would be motivated to produce various pharmaceutically acceptable salts in order to achieve the desired properties of the pharmaceutical agent. Pharmaceutically acceptable salts of organoboronic acids salts include alkaline metal salts, alkaline earth metal salts (including calcium) and amine salts (Adams et al. US 5,780,454; column 9, lines 57-65). In the absence of some unexpected properties for the base addition salts of organoboronic acids of the instantly claimed compounds, the invention is seen to be prima facie obvious in view of the prior art of record and the case law cited herein.

Response to applicants' remarks

Applicants arguments were not found convincing. Applicants' showing of unexpected results particularly the increased stability of the boronic acid salts compared to the boronic acid is not commensurate in scope with the claimed invention. Please note that the claimed invention reads on all salts of the boronic acid and numerous compounds encompassed by the general structure of claim 1, whereas applicant has demonstrated superior properties in just 2 salts. Its not reasonable to assume that these properties will extend to all salt of boronic acids.

Furthermore, the examiner is maintaining the position that choosing salts of a pharmaceutically active compound in order to improve the properties such as stability, hygroscopicity and flowability of the said compound is well within purview of one of ordinary skill in the art. Applicants' argument that the boronic acids are known to be unstable provides further motivation for one of ordinary skill in the art to form a salt of the said acid.

Double Patenting

Claims 1-23, 26-28 and 30-64 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-21, 23, 25, 50-56 and 71-73 of U.S. Patent No. 7,112,572 ('572). Although the conflicting claims are not identical, they are not patentably distinct from each other because the all the limitations of the instant claims are found in the sited claims of ('572).

Instant claims are directed to a pharmaceutically acceptable base addition salt of a boronic acid of formula (I) in claim 1, or formula (II) in claim 14, to formulation of the said salt in claims 26-28, pharmaceutical formulations in claims 50-56, anhydride comprising salts in claims 71-73.

Claim 2 of '572 claims a structure that encompasses the structure of the instant claim 1. Claim 12 of '572 displays a structure that is identical compound of formula (II) in the instant claim 14. Claims of '572 that directed to a salt and are dependent on claims 2 and 12 have all of the limitations of the instant claims 1-23 and 30-38. The formulations and medicament claimed in the instant claims 26-28 are obvious over claims 20, 23 and 25 of '572. The said formulation and medicament claims differ from the instant invention in that the compounds from which the formulation and medicament is made are not identical to the compound in '572. However, compound (III) of '572 encompasses all of the instantly claimed compounds, and compound (IV) of '572 is specie of the instantly claimed compound (I).

References made of record but not relied upon in the office action

Berge et al. *Journal of pharmaceutical sciences*, 1977, 66(1), pages 1-19

Conclusion

Claims 1—64 are pending


Claims 1-23, 26-28 and 30-64 are rejected

Claims 24, 25 and 29 are withdrawn.

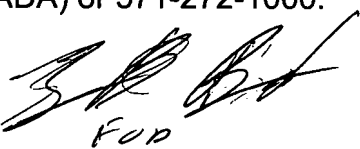
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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